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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/543,771	04/05/2000	John P. Caruth	032796-014	6685

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EXAMINER
KAUSHAL, SUMESH

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1636	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/543,771	Applicant(s) CARULLI ET AL.	
	Examiner S. Kaushal	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 24-29* is/are pending in the application.

4a) Of the above claim(s) *2-13,24 and 25* is/are withdrawn from consideration.

5)☒ Claim(s) *1* is/are allowed.

6)☒ Claim(s) *14-19,26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response filed on 04/25/02 has been acknowledged.

Claims 20-23 were canceled.
Claims 26-29 were newly filed.
Claims 1-19 and 24-29 were pending

This application contains claims 2-13 and 24-25 are drawn to an invention non-elected with traverse in Paper No. 13. A complete reply to the final rejection must include cancelation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1, 14-19 and 26-29 were examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

▶ *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED.*

Claim Rejections - 35 USC § 101

In response to applicant's remarks filed on Paper No: 17 (04/25/02) pages 2-12 the rejection under 35 USC 101 is withdrawn. The amino acid sequences of SEQ ID NO:4 (HBM) is an allelic variant of Zmax1 (wild type) protein. The point mutation present in HBM (locus 171 G to V) causes increase in bone density in HBM-affected individuals.

Claim Rejections - 35 USC § 112

Claims 14-19 and 26-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the same reasons of record as set forth in the earlier official action mailed on the 10/26/01.

The applicant argues that similarity between LDLR and HBM dose not negate the evidence provided in the specification that individuals expressing HBM protein are protected from diseases such as osteoporosis (response, page 13, ¶ 3). The applicant further argues that to comply with enablement requirement the specification need not to disclose any working example, if the invention could be practiced without undue amount of experimentation (response, page 14, ¶ 1). The applicant further argues that one skill in the art could easily purify the extracellular domain of the receptor without undue experimentation (response, page a4, ¶ 2). The applicant further argues that the specification need not to specify the dosage or method of use if it is known that one skill in the art could obtain such information without undue experimentation (response, page 14, ¶ 3).

However, this is found unpersuasive because applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The invention as claimed is drawn to a method of a of

altering bone development in host comprising administering the amino acid of SEQ ID NO:4 to a Somatic cell and/or Germ-line cell of a host suffering from a bone development disorder The claims are further drawn to a method of treating osteoporosis comprising administering the i) amino acid of SEQ ID NO:4 , ii) the extracellular domain of the amino acid of SEQ ID NO:4 and iii) intracellular domain of the amino acid of SEQ ID NO:4. However, the instant specification fails to provide a single working example that establishes that the administration administering the i) HBM ii) the extracellular domain of HBM or iii) intracellular domain HBM leads to bone development and/or the treatment of osteoporosis in any and all vertebrates.

The courts have clearly stated that: "A specification did not disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). A general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997).

In instant case the specification fails to provide any guidance regarding the role of amino acid of SEQ ID NO:4 in the bone development and/or osteoporosis. The art at the time of filing teaches that the development of bones is not only polygenic but is also affected by various growth factors, hormones, nutrient uptake and pathogens. The strength and integrity of bones depends on maintaining a delicate balance between bone re-absorption by osteoclasts and bone formation by osteoblasts. With aging or as a result of disease, this delicate balancing act becomes tipped in favor of osteoclasts so that bone resorption exceeds bone formation, rendering bones brittle and prone to fracture. (Radan et al, Science 289:1508-1514, 2000, abstract).

The osteoporosis is a multifactorial disorder characterized by low bone mass and micro architectural deterioration of bone structure. The incidence of osteoporosis is higher in women than in men and increases sharply after 50 yrs of age. Recent studies reveled that genetic factors

plays an important role in the pathogenesis of osteoporosis and the segregation analysis reveled that bone mineral density is under polygenic control (Kundu et al, Peptides 20:523-537, 1999. page 523, col.1-2). The most common cause of osteoporosis in women is the decrease in estrogen that accompanies menopause. Estrogen loss is associated with elevated bone resorption caused by a rise in osteoclast number, which is driven by increases in the cytokines that regulate osteoclast generation (RANK-ligand, TNF-a, IL-1, IL-6, IL-11, M-CSF and prostaglandin E). Production of all of these cytokines is either directly or indirectly suppressed or regulated by estrogen (Rodan, page 1509, col.1, para. 3).

Several hormones also regulate the bone mineralization and demineralization, primarily by parathyroid hormone (PTH). The higher concentration of PTH inhibits the bone formation whereas the low serum concentration increases the bone mass (Kundu et al page 524, col. 2, sec. 4.1; Ziegler et al, Steroids 63:344-348, 1998, page 345, fig-1). In addition, bone formation is also affected by nutrient uptake. The reduced caloric intake is associated with reduced calcium intake which results in decrease in bone mass over time (Bollag et al, Endocrinology, 141(3)1228-35, 2000, page 1234, col.1 para.2).

Considering the multifactorial nature of bone development and osteoporosis, the specification fails to teach effect of HBM protein (SEQ ID NO:4) on osteoblast or osteoclast activity. At best the specification (figures 10-13) discloses the cellular localization of Zmax transcripts in both osteoblast/osteoclast cells. The specification fails to disclose that the administration of HBM protein leads to any change in osteoblast (increase) or osteoclast (decrease) activity that results in bone formation. In addition, in view of instant specification it is even unclear that HBM-protein modulates any hormone like PTH that regulates bone development. Similarly, the specification fails to disclose that HBM affects estrogen levels and/or its activity, or cytokines that affects osteoclast number or their activity.

The official sequence search reveled that the amino acid sequences of SEQ ID NO:4 matches 99.6% to the amino acid sequence of a Low Density Lipoprotein Receptor Related Protein (LRP5) expressed in hepatocytes and adrenal cortex and is know to play a key role in the hepatic clearance of cholesterol carrying LDL (Kim et al, J Biochem. (Tokyo) 124:1072-1076, 1998, page 1072, col.1). Considering the high amino acid sequence homology (99.6%) one skill in the art would conclude that the amino acid sequence of SEQ ID NO:4 falls in the realm of

LDL-receptor-related-protein family that would regulate hepatic clearance of cholesterol carrying LDL. Since the specification fails disclose a single working example that teaches the polypeptides of SEQ ID NO:4 regulates bone formation, it is unclear how one skill in the art would use the SEQ ID NO:4 to alter bone development and/or osteoporosis.

In addition the invention as claimed is drawn to a method wherein the amino acid sequences of SEQ ID NO:4 is administered to a somatic and/or a germ-line cell. It is unclear how the administration of the polypeptide (as claimed) into somatic and/or a germ-line cell would later effects the bone development and or treat osteoporosis. The state of art at the time of filing teaches that proteins or drugs that modulates bone development and/or osteoporosis are administered systemically into patients to initiate the cascade of bone formation. The specification fails to teach the targeted delivery of HBM polypeptide to a cell involved in the bone development. The HBM polypeptide as claimed belongs to LDL-receptor-related-protein family that regulates hepatic clearance of cholesterol carrying LDL. It is unclear how one skill in the art would specifically target the membrane of bone cells in vivo so that the administered HBM-receptor takes over endogenous Zmax1 functions. It is unclear how the administration of intercellular domain in vivo would modify the interacellular signal transduction of bone cells, which result in HBM phenotype. Furthermore, the administration of extracellular domain alone would be non-productive as it only completes with a natural ligand for HBM receptor protein. The specification fails to disclose a natural ligand for the extracellular domain of HBM-receptor protein, blocking of which regulates the bone formation. At best the only know ligand for thee SEQ ID NO: 4 would be LDL (see Kim et al) and it is unclear how one skill in the art would regulate bone development and or osteoporosis by blocking LDL activity.

Furthermore, the specification fails to disclose that whether the high bone mass (HBM) phenotype is the result of the loss of Zmax1 protein activity or is the result of altered Zmax1 protein function due to the HBM mutation. The polypeptide as claimed appears to be a receptor comprising extracelluar and interacelluar domains. It is unclear how one skill in the art would purify the receptor (as claimed) in an active and soluble form, which upon administration to a subject would not loose its specific activity due to in vivo degradation. Similarly, it is unclear how one skill in the art would use the polypeptide wherein the interacellular domain is involved in a signal transduction mechanism. The specification fails disclose the role of HBM in any

signal transduction pathway, that leads to bone development. It is unclear what is the target tissue for the polypeptide as claimed. It is even unclear whether the HBM polypeptide affects osteoblast/osteoclast activity or modulates a hormone like PTH, which regulates bone development.

In addition HBM protein based therapy to induce bone development and/or treat osteoporosis is not considered routine in the art and without sufficient guidance to a specific mechanism by which the HBM affects the bone development the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The amount of experimentation required would include administration of the amino acid sequence of SEQ ID NO:4, extracellular or intercellular domain of SEQ ID NO:4 into patients suffering from any and all bone defects (Osteoporosis, Paget disease, Bone cancer, Inflammatory bone disease etc) and the evaluation of bone development.

Conclusion

Claim 1 is allowed.

Claims 14-19 and 26-29 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem.Yucel can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

S. Kaushal
Patent examiner

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER